Remarks

Claims 95-104, 106-131 and 133-138 are pending in the subject application and currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the objection to the claim and the rejections under 35 U.S.C. § 112, first and second paragraphs.

At the outset, Applicants note the arguments, at page 4, that the limitation "derivative" allows for a broader interpretation of the claims. Applicants note that although claim 95 contains the limitation "derivative," the claims are limited to chemical derivatives of the claimed sequences (*e.g.*, consisting of SEQ ID NOs: 6, 8 or 13) in light of the specification. Specifically, Applicants point to specification at page 14, lines 6-11, where the term "derivative" is defined as "derivatives which can be prepared from the functional groups present on the lateral chains of the amino acid moieties or on the N-/ or C-terminal groups according to known methods. Such derivatives include for example esters or aliphatic amides of the carboxyl-groups and N-acyl derivatives of free amino groups or O-acyl derivatives of free hydroxyl-groups and are formed with acyl-groups as for example alcanoyl- or aroyl-groups." Thus, the broadest reasonable interpretation of the claims in subsection g) of claim 95 would be one of the claimed amino acid sequences derivatized on functional groups within the polypeptide.

Claims 95-104, 106-131 and 133-136 remain rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991). The Office Action dated January 22, 2009 asserts at page 12, that:

> By employing the methods of Chien *et al.*, a person of ordinary skill in the art would have necessarily arrived to the domains that are essential to the binding of ACT 4L (i.e., OX40L) to its receptor because the domain to be searched was disclosed by Godfrey *et. al.* (51-183 of the OX40L) so that the search would have entailed a finite number of fragments, already envisioned (in length) perfectly feasible within the technical grasp of ordinary skill in the art which read the references as a whole.

The Office Action dated July 6, 2009 repeats this "the obvious to try" reasoning, stating that "a skilled artisan [would use] known options available to him to optimize a process or a formulation" to arrive at the claimed polypeptide.

Applicants respectfully request reconsideration. In *KSR*, the Supreme Court stated that an invention may be found obvious if it would have been obvious to a person having ordinary skill to try a course of conduct. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 41 (2007). However, "an invention would not have been obvious to try when the inventor would have to try all possibilities in a field unreduced by direction of the prior art, . . . where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Bayer Schering Pharma AG. v. Barr Lab., Inc.*, 91 USPQ2d 1565, 72-73 (Fed. Cir. 2009), *In re O'Farrell*, 853 F.2d 894 (Fed. Cir, 1988). Such interpretation is consistent with *KSR* that prior art has to provide "a finite number of identified, predictable solutions," where the number of options to be "small or easily traversed," in order to render an invention obvious. *KSR International Co. v. Teleflex Inc.* at 1742, *Bayer Schering Pharma AG.* at 1573.

The as-filed application discloses (and claims) novel OX40L-derived polypeptide fragments that exhibit surprisingly high binding affinity with OX40L receptors (specification at page 4, lines 11-16). Specifically, the claimed polypeptide contains: i) a 31-amino acid sequence represented by SEQ No: 6; ii) a sequence where one or more amino acids of SEQ ID: 6 have been deleted and the sequence contains a 5-amino acid sequence represented by SEQ ID NO: 13; iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1 which still contain SEQ ID NO: 13; iv) a 10-amino acid sequence represented by SEQ ID NO: 8 or a 5-amino acid sequence represented by SEQ ID NO: 13; and v) an active mutant, fusion peptide, conjugate or derivative of/containing the above sequences (claim 1). Advantageously, the claimed small molecule polypeptides demonstrate superior inhibition effect against OX40R-OX40L binding interaction, thus capable of targeting the OX40R pathway and inhibiting aberrant or undesirable physiological events under its control (specification at page 37, lines 16-20).

In contrast, Godfrey *et al.* relate to purified extracellular domain of ACT-4-L polypeptides (OX40L) consisting of 183 amino acids (Godfrey *et al.* claim 1, SEQ ID No: 4). Although Godfrey *et al.* state that the polypeptides can be either in full length or in fragments, no specific peptide

fragments other than the full length peptide is ever disclosed or suggested. Indeed, the polypeptide claimed by Godfrey *et al.* is directed only to a sequence represented by the full length of SEQ ID No: 4, which consists of 183 amino acids. In addition, Goldfrey *et al.* do not teach or suggest that a small molecule peptide derived from OX40L would possess superior binding affinity to OX40 receptor nor is there any indication as to which fragment would possess satisfactory binding affinity. Thus, a small molecule peptide having an amino acid sequence identical or similar to the claimed invention is neither taught nor suggested in Godfrey *et al.*

The Office Action dated July 6, 2009 asserts at page 3 that "the polypeptide of SEQ ID NO: 6 is 100% identical with the amino acid string 94-124 of the SEQ. ID. No. 4 of Godfrey *et al.* Also, SEQ ID NO: 6 of the instant Application comprises the SEQ ID NO: 8 and 13 and these sequences would have been found by applying the teachings of the references cited"; thus, claims are obvious in view of Godfrey *et al.* Applicants respectfully note that, first, Godfrey *et al.* merely teach the purified OX40L in full length. While thousands or tens of thousands of possible fragments could be generated from the full length OX40L protein, Godfrey *et al.* however provide no guidance as to which peptide fragment might possess satisfactory binding affinity.

More importantly, the small molecule peptide fragment in the claimed invention is not a random derivation from the 183-amino acid full length OX40L protein in Godfrey *et al.* Even for peptides with overlapping sequences, the respective binding affinity is highly unpredictable. As demonstrated in Example 2 of the as-filed application, a peptide corresponding to amino acids 107-116 (P5-1) is capable of inhibiting the binding of OX40R to OX40L in the micromolar range (K_d about10 and 62 micromolar respectively); however, other peptides, such as amino acids 107-124, 99-108 or 111-120, from the same region represented by amino acids 94-124 of the OX40L sequence show no or hardly any measurable effect on OX40R-OX40L interaction (specification at 36, lines 5-10; Figure 6B). Thus, absent of any indication as to which peptide fragment is critical to try, one skilled in the art would have to try what amounts to an infinite number of peptides generated from the full length OX40L protein. Such a lack of direction in the prior art hardly meets the *KSR* "obvious to try" standard, which requires the prior art to provide "a finite number of identified, predictable solutions."

Applicants further note that the secondary reference, Chien *et al.*, taken as a whole, does not provide a remedy to the deficiency of Godfrey *et al.* noted above. Chien *et al.* relate to a method for detecting protein-protein interaction by DNA binding and transcriptional activation *in vivo* (Chien *et al.* at page 9578) of random genomic libraries (see page 9579, column 1, construction and screening of genomic/domain libraries). Specifically, one protein (X; a known protein) is fused with a DNA-binding domain, while an unknown protein (Y) is fused with a DNA activation domain; the interaction/dimerization of the two proteins allows the DNA binding domain to localize in proximity with the DNA activation domain, thereby initiating transcription of a reporter gene *in vivo* to produce detectable signals. However, there is no indication that Chien *et al.* would be a reliable model for detecting OX40L fragments in the claimed invention. For example, it is possible that the complex of the OX40L peptide and its receptor would be too large to allow for the interaction of the activation and binding domains of GAL4. In view of the above indeterminate parameters, those skilled in the art are unlikely to utilize the Chien *et al.* methodology with a reasonable expectation of success.

In addition to Chien *et al.*, the Office Action dated July 6, 2009 at page 4 further asserts that in conjunction with the teachings in Godfrey *et al.*, both Scarborough *et al.* and Sokoloff *et al.* also evidence the state of art that would allow those skilled in the art to arrive at the claimed invention. Applicants respectfully note that both of these references, while cited as evidence in this matter, appear to be improperly relied upon in an effort to buttress the obviousness rejection of record. While it is acknowledged that the Patent Office can rely upon such references when articulating a rejection, it is respectfully submitted that the reliance on such references to provide motivation to reject a claimed invention and making that rejection final is improper. Thus, Applicants respectfully request that the finality of the last office action be withdrawn.

Additionally, the state of the art as evidenced by Sokoloff *et al.* and Scarborough *et al.* would not remedy the deficiencies noted in Godfrey *et al.* There is no specific teaching of any particular method that would reduce the potentially infinite pool of peptide fragments or provide the direction lacking in Godfrey *et al.* to the claimed peptide; thus, the *KSR* "obvious to try" standard, which requires the prior art to provide "a finite number of identified, predictable solutions," is not satisfied. Therefore, in view of the infinite pool of potential protein fragments, the unpredictable nature of peptide binding affinity, in conjunction with the lack of direction in all of the references cited, it is

respectfully submitted that a *prima facie* case of obviousness has not been established for the claimed invention and those skilled in the art would not have had a reasonable expectation of success to arrive at the claimed invention. Accordingly reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested as a *prima facie* case of obviousness has not been established in this matter.

Claim 137 remains rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991) and Hruby *et al.* (2000). Applicants respectfully assert that the claimed invention is not obvious over the cited references. The Office Action dated July 6, 2009 repeats the position that Hruby *et al.* teach that "although native biologically active peptides have a great potential for medical applications, they often need to be modified to overcome certain problems inherent in current drug-delivery strategies;" thus, together with teachings in Godfrey *et al.* and Chien *et al.*, claim 137 is obvious (Office Action dated January 22, 2009 at pages 13-14; Office Action dated July 6, 2009 at page 5).

Applicants respectfully point out that Hruby *et al.* fail to remedy the deficiencies noted in Godfrey *et al.* and Chien *et al.* Even if there is a need to modify native biologically active proteins, the cited prior art has not provided any teaching or suggestion regarding how to solve such need with an expectation of success. Indeed, Hruby *et al.* explicitly acknowledge the prior art's failure in solving such need, stating that "the proper choice of template that can place the key side chain residue in 3D space is still difficult, and thus only partial success has been achieved in terms of potent and selective ligands" (Hruby *et al.* Abstract). Thus, teachings of Hruby *et al.* actually indicate that the claimed invention, which successfully solves a long-felt need in the art is unobvious over the cited references. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claim 138 remains rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991) and Quillan *et al.* (U.S. Patent No. 6,602,856). Applicants respectfully assert that Quillan *et al.* fail to remedy the deficiencies of Godfrey *et al.* and Chien *et al.*, thus, claim 138 is not obvious over the cited references. As is acknowledged in the Office Action date January 22, 2009, Quillan *et al.* only teach a method of adding blocking groups to target peptides by acetylation or carboxylation. However, as discussed above, in light of the

teachings in the references cited, those skilled in the art would not even have derived the claimed peptides; thus, whether acetylation or carboxylations is taught becomes irrelevant in the obviousness determination. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

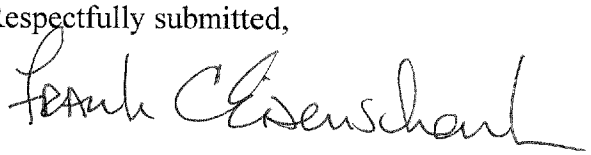
Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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